



PATENT
Attorney Docket No. 3495.0010-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
)
Marc Alizon, et al.)
)
Serial No.: 07/158,652) Group Art Unit: 1805
)
Filed: February 22, 1988) Examiner: J. Railey
)
For: CLONED DNA SEQUENCES RELATED)
TO THE GENOMIC RNA OF)
LYMPHADENOPATHY ASSOCIATED)
VIRUS (LAV) AND PROTEINS)
ENCODED BY SAID LAV GENOMIC)
RNA)

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

CLAIM FOR PRIORITY

Under the provisions of Section 119 of 35 U.S.C.,
applicants hereby claim the benefit of the filing date of Great
Britain Application No. 84 29099, filed November 16, 1984, for
the above identified United States Patent Application.

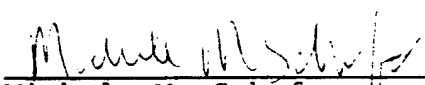
In support of applicants' claim for priority, filed
herewith is one certified copy of GB 84 29099.

If there are any fees due in connection with the filing of
this Paper, please charge such fees to our Deposit Account
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Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER

By:


Michele M. Schäfer
Reg. No. 34,717

Date: October 21, 1993



THE PATENT OFFICE,
25 SOUTHAMPTON BUILDINGS,
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I, the undersigned, being an officer duly authorised in accordance with Section 62(3) of the Patents and Designs Act 1907, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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PATENTS ACT 1977

16 NOV 1984

PATENTS FORM No. 1/77 (Revised 1982)
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19/11/84 B3662 PAT*** 10.0

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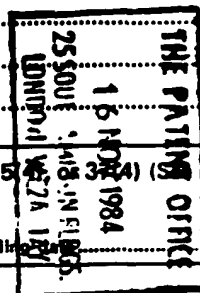
29099

REQUEST FOR GRANT OF A PATENT

8429099

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I	Agent's Reference	JJD/EAF/26804
II	Title of Invention	CLONED DNA SEQUENCES RELATED TO THE GENOMIC RNA OF LYMPHADENOPATHY-ASSOCIATED VIRUS (LAV) AND PROTEINS ENCODED BY SAID LAV GENOMIC RNA.
III	Applicant or Applicants (See note 2)	
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IV	Inventor (see note 3)	or (b) A statement on Patents Form No. 7/77 is/will be furnished
V	Name of Agent (if any) (See note 4)	Reddie & Grose
	ADP CODE NO	
VI	Address for Service (See note 5)	16 Theobalds Road London WC1X 8PL
VII	Declaration of Priority (See note 6)	
	Country	Filing date
	File number	
VIII	The Application claims an earlier date under Section 8(3), 12(6), 15(4) or 31(4) (See note 7)	
	Section No.	
	Earlier application or patent number	and filing date



IX Check List (To be filled in by applicant or agent)

- | | |
|---|---|
| A The application contains the following number of sheet(s) | B The application as filed is accompanied by:- |
| 1 Request 1 Sheet(s) | 1 Priority document No |
| 2 Description 17 Sheet(s) | 2 Translation of priority document No |
| 3 Claim(s) 2 Sheet(s) | 3 Request for Search No |
| 4 Drawing(s) 26 Sheet(s) | 4 Statement of Inventorship and Right to Apply No |
| 5 Abstract 0 Sheet(s) | 5 |

X It is suggested that Figure No 1 of the drawings (if any) should accompany the abstract when published.

XI Signature (See note 8)


Reddie & Grosse, Agents for the Applicant(s)

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings. ✓
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd," are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.
5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
6. The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
7. When an application is made by virtue of section 8(3), 12(8), 15(4), or 37(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
8. Attention is directed to rules 90 and 106 of the Patent Rules 1982.
9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.
10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

Cloned DNA sequences related to the genomic RNA of lymphadenopathy-associated-virus (LAV) and proteins encoded by said LAV genomic RNA

The invention relates to cloned DNA sequences indistinguishable from genomic RNA and DNA of lymphadenopathy-associated virus (LAV), a process for their preparation and their uses. It relates more particularly to stable probes including a DNA sequence which can be used for the detection of the LAV virus or related viruses or DNA proviruses in any medium, particularly biological samples containing any of them. The invention also relates to polypeptides, whether glycosylated or not, encoded by said DNA sequences.

Lymphadenopathy-associated virus (LAV) is a human retrovirus first isolated from the lymph node of a homosexual patient with lymphadenopathy syndrome, frequently a prodrome or a benign form of acquired immune deficiency syndrome (AIDS). Subsequently other LAV isolates have been recovered from patients with AIDS or pre-AIDS. All available data are consistent with the virus being the causative agent of AIDS.

A method for cloning such DNA sequences has already been disclosed in British Patent Application No. 84 23858 filed on September 19, 1984. Reference is hereafter made to that application as concerns subject matter in common with the further improvements to the invention disclosed herein.

The present invention aims at providing additional new means which should not only also be useful for the detection of LAV or related viruses (hereafter more generally referred to as "LAV viruses"), but also have more versatility, particularly in detecting specific parts of the genomic DNA of said viruses whose expression products are not always directly detectable by immunological methods.

The present invention further aims at providing

polypeptides containing sequences in common with polypeptides encoded by the LAV genomic RNA. It relates even more particularly to polypeptides comprising antigenic determinants included in the proteins encoded and expressed by the LAV genome occurring in nature. An additional object of the invention is to further provide means for the detection of proteins related to LAV virus, particularly for the diagnosis of AIDS or pre-AIDS or, to the contrary, for the detection of antibodies against the LAV virus or proteins related therewith, particularly in patients afflicted with AIDS or pre-AIDS or more generally in asymptomatic carriers and in blood-related products. Finally the invention also aims at providing immunogenic polypeptides, and more particularly protective polypeptides for use in the preparation of vaccine compositions against AIDS or related syndroms.

The present invention relates to additional DNA fragments, hybridizable with the genomic RNA of LAV as they will be disclosed hereafter, as well as with additional cDNA variants corresponding to the whole genomes of LAV viruses. It further relates to DNA recombinants containing said DNAs or cDNA fragments.

The invention relates more particularly to a cDNA variant corresponding to the whole of LAV retroviral genomes, which is characterized by a series of restriction sites in the order hereafter (from the 5' end to the 3' end).

The coordinates of the successive sites of the whole LAV genome (restriction map) are indicated hereafter too, with respect to the Hind III site (selected as of coordinate 1) which is located in the R region. The coordinates are estimated with an accuracy of ± 200 bp :

	Hind III	0
	Sac I	50
35	Hind III	320
	Pst I	800
	Hind III	1 100

	Bgl II	1 300
	Kpn I	3 500
	Kpn I	3 900
	Eco RI	4 100
5	Eco RI	5 300
	Sal I	5 500
	Kpn I	6 100
	Bgl II	6 500
	Bgl II	7 600
10	Hind III	7 850
	Bam HI	8 150
	Xho I	8 800
	Kpn I	8 700
	Bgl II	8 750
15	Bgl II	9 150
	Sac I	9 200
	Hind III	9 250

Another DNA variant according to this invention optionally contains an additional Hind III approximately at the 5 550 coordinate.

Reference is further made to fig. 1 which shows a more detailed restriction map of said whole-DNA (λ J19).

An even more detailed nucleotide sequence of a preferred DNA according to the invention is shown in fig. 4-12 hereafter.

The invention further relates to other preferred DNA fragments which will be referred to hereafter.

Additional features of the invention will appear in the course of the non-limitative disclosure of additional features of preferred DNAs of the invention, as well as of preferred polypeptides according to the invention. Reference will further be had to the drawings in which :

- fig. 1 is the restriction map of a complete LAV genome (clone λ J19) ;

- figs. 2 and 3 show diagrammatically parts of the three

possible reading phases of LAV genomic RNA, including the open reading frames (ORF) apparent in each of said reading phases ;

- figs. 4-12 show the successive nucleotidic sequences of a complete LAV genome. The possible peptidic sequences in relation to the three possible reading phases related to the nucleotidic sequences shown are also indicated ;
- figs. 13-18 reiterate the sequence of part of the LAV genome containing the genes coding for the envelope proteins, with particular boxed peptidic sequences which corresponds to groups which normally carry glycosyl groups.

The sequencing and determination of sites of particular interest was carried out on a phage recombinant corresponding to AJ19 disclosed in the above-said British Patent application Nr. 84 23859. A method for preparing it is disclosed in that application.

The whole recombinant phage DNA of clone AJ19 (disclosed in the earlier application) was sonicated according to the protocol of DEININGER (1983), Analytical Biochem. 129, 218. the DNA was repaired by a Klenow reaction for 12 hours at 16°C. The DNA was electrophoresed through 0.8 % agarose gel and DNA in the size range of 300-800 bp was cut out and electroeluted and precipitated. Resuspended DNA (in 10 mM Tris, pH 8 ; 0.1 mM EDTA) was ligated into M13mp8 RF DNA (cut by the restriction enzyme SmaI and subsequently alkaline phosphated), using T4 DNA- and RNA-ligases (Maniatis T et al (1982) - Molecular cloning - Cold Spring Harbor Laboratory). An *E. coli* strain designated as TGI was used for further study. This strain has the following genotype :

Alac pro, supE, thi.F'traD36, proAB, lacI^q, ZAM15,r⁻

This *E. coli* TGI strain has the peculiarity of enabling recombinants to be recognized easily. The blue colour of the cells transfected with plasmids which did

not recombine with a fragment of LAV DNA is not modified. To the contrary cells transfected by a recombinant plasmid containing a LAV DNA fragment yield white colonies. The technique which was used is disclosed in Gene (1983), 28.

5 101.

This strain was transformed with the ligation mix using the Hanahan method (Hanahan D (1983) J. Mol. Biol. 168, 557). Cells were plated out on tryptone-agarose plate with IPTG and X-gal in soft agarose. White plaques were
10 either picked and screened or screened directly in situ using nitrocellulose filters. Their DNAs were hybridized with nick-translated DNA inserts of pUC18 Hind III subclones of AJ19. this permitted the isolation of the plasmids or subclones of λ which are identified in the
15 table hereafter. In relation to this table it should also be noted that the designation of each plasmid is followed by the deposition number of a cell culture of E. coli TGI containing the corresponding plasmid at the "Collection Nationale des Cultures de Micro-organismes" (C.N.C.M.) of
20 the Pasteur Institute in Paris, France. A non-transformed TGI cell line was also deposited at the C.N.C.M. under Nr. I-364. All these deposits took place on November 15, 1984. The sizes of the corresponding inserts derived from the LAV genome have also been indicated.

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TABLE
Essential features of the recombinant plasmids

5	- pJ19 - 1 plasmid	(I-365)	0.5 kb
	Hind III - Sac I - Hind III		
10	- pJ19 - 17 plasmid	(I-367)	0.6 kb
	Hind III - Pst I - Hind III		
	- pJ19 - 6 plasmid	(I-368)	1.5 kb
15	Hind III (5')		
	Sam HI		
	Xho I		
	Kpn I		
	Bgl II		
20	Sac I (3')		
	Hind III		
	- pJ19-13 plasmid	(I-368)	6.7 kb
25	Hind III (5')		
	Bgl II		
	Kpn I		
	Kpn I		
	Eco RI		
30	Eco RI		
	Sal I		
	Kpn I		
	Bgl II		
	Bgl II		
35	Hind III (3')		

M : méthionine
 W : tryptophan
 F : phenylalanine
 Y : tyrosine
 5 L : leucine
 V : valine
 I : isoleucine
 G : glycine
 Y : thréonine
 10 S : serine
 E : glutamic acid
 D : Aspartic acid
 N : asparagine
 Q : glutamine
 15 P : proline.

The asterik signs "*" correspond to stop codons (i.e. TAA, TAG and TGA).

Starting above the first line of the DNA nucleotidic sequence of fig. 4 the three reading phases
 20 are respectively marked "1", "2", "3", on the left handside of the drawing. The same relative presentation of the three theoritical reading phases is then used all over the successives lines of the LAV nucleotidic sequence.

Figs. 2 and 3 provide a diagrammatized representation of the lengths of the successive open reading
 25 frames corresponding to the successive reading phases (also referred to by numbers "1", "2" and "3" appearing in the left handside part of fig. 2). The relative positions of these open reading frames (ORF) with respect to the
 30 nucleotidic structure of the LAV genome is referred to by the scale of numbers representative of the respective positions of the corresponding nucleotides in the DNA sequence. The vertical bars correspond to the positions of the corresponding stop codons.

35 1) The "gag gene" (or ORF-gag)

The "gag gene" codes for core proteins.

Particularly it appears that a genomic fragment (ORF-gag) thought to code for the core antigens including the p25, p18 and p13 proteins is located between nucleotidic position 238 (starting with 5' CTA GCG GAG 3') and
 5 nucleotidic position 1759 (ending by CTCG TCA CAA 3'). The structure of the peptides or proteins encoded by parts of said ORF is deemed to be that corresponding to phase 2.

The methionine aminoacid "M" coded by the ATG at position 280-282 is the probable initiation methionine of
 10 the gag protein precursor. The end of ORF-gag and accordingly of gag protein appears to be located at position 1759.

The beginning of p25 protein, thought to start by a P-I-V-Q-N-I-Q-G-Q-M-V-M aminoacid sequence is
 15 thought to be coded for by the nucleotidic sequence CCTATA.... starting at position 858.

Hydrophilic peptides in the gag open reading frame are identified hereafter. They are defined starting from aminoacid 1 = Met (M) coded by the ATG starting from 260-2
 20 in the LAV DNA sequence.

Those hydrophilic peptides are
 12-32 aminoacids inclusive

	37-46	-	-
	49-79	-	-
25	88-153	-	-
	158-189	-	-
	178-188	-	-
	200-220	-	-
	226-234	-	-
30	239-284	-	-
	288-331	-	-
	352-381	-	-
	377-390	-	-
	399-432	-	-
35	437-484	-	-
	482-498	-	-

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sequences of the env gene as represented in figs. 13-18 involves first reading the first line at the top of fig. 13 then proceeding further with the first line of fig. 14. One then returns to the beginning of the second line of fig. 13, then again further proceed with the reading of the second line of page 14, etc... The same observations then apply to the reading of the paired figs. 15 and 16, and paired figs. 17 and 18, respectively.

The locations of neutralizing epitopes are further apparent in figs. 13-18. reference is more particularly made to the boxed groups of three letters included in the aminoacid sequences of the envelope proteins (reading phase 3) which can be designated generally by the formula N-X-S or N-X-T, wherein X is any other possible aminoacid. Thus the initial protein product of the env gene in a glycoprotein of molecular weight in excess of 91,000. These groups are deemed to generally carry glycosylated groups. These N-X-S and N-X-T groups with attached glycosylated groups form together hydrophylic regions of the protein and are deemed to be located at the periphery of and to be exposed outwardly with respect to the normal conformation of the proteins. Consequently they are considered as being epitopes which can efficiently be brought into play in vaccine compositions.

The invention thus concerns with more particularly peptide sequences included in the env-proteins and excizable therefrom (or having the same aminoacid structure), having sizes not exceeding 200 aminoacids.

Preferred peptides of this invention (referred to hereafter as a, b, c, d, e, f) are deemed to correspond to those encoded by the nucleotide sequences which extend respectively between the following positions :

- a) from about 8085 to about 8200
- b) " " 8280 " " 8310
- 35 c) " " 8390 " " 8440
- d) " " 8465 " " 8620

e) " " 6860 " " 6930
 f) " " 7535 " " 7630

Other hydrophilic peptides in the env open reading frame are identified hereafter. they are defined starting from
 5 aminoacid 1 = lysine (K) coded by the AAA at position 5670-2 in the LAV DNA sequence.

These hydrophilic peptides are
 8-23 aminoacids inclusive

10	63-78	"	"
	82-90	"	"
	97-123	"	"
	127-183	"	"
	197-201	"	"
15	239-294	"	"
	300-327	"	"
	334-381	"	"
	397-424	"	"
	488-500	"	"
20	510-523	"	"
	551-577	"	"
	594-603	"	"
	621-630	"	"
	657-679	"	"
25	719-758	"	"
	780-803	"	"

The invention also relates to any combination of these peptides.

4) The other ORF

30 The invention further concerns DNA sequences which provide open reading frames defined as ORF-Q, ORF-R and as "1", "2", "3", "4", "5", the relative position of which appears more particularly in figs. 2 and 3.

These ORFs have the following locations :

35	ORF-Q	phase 1	start 4478	stop 5086
	ORF-R	" 2	" 8249	" 8896

ing
ing

13

ORF-1	-	1	-	5029	-	5316
ORF-2	-	2	-	5273	-	5515
ORF-3	-	1	-	5383	-	5616
ORF-4	-	2	-	5519	-	5773
5 ORF-5	-	1	-	7986	-	8279

The LTR (long terminal repeats) can be defined as lying between position 8560 and position 180 (and extending over position 9097/1). As a matter of fact the end of the genome is at 9097 and, because of the LTR structure of the retrovirus, links up with the beginning of the sequence :

Hind III

CTCAATAAAGCTTGCTTG



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9097 1

The invention concerns more particularly all the DNA fragments which have been more specifically referred to hereabove and which correspond to open reading frames. It will be understood that the man skilled in the art will be able to obtain them all, for instance by cleaving an entire DNA corresponding to the complete genome of a LAV species, such as by cleavage by a partial or complete digestion thereof with a suitable restriction enzyme and by the subsequent recovery of the relevant fragments. The different DNAs disclosed in the earlier mentioned British Application can be resorted to also as a source of suitable fragments. The techniques disclosed hereabove for the isolation of the fragments which were then included in the plasmids referred to hereabove and which were then used for the DNA sequencing can be used.

Of course other methods can be used. Some of them have been exemplified in the earlier British Application. reference is for instance made to the following methods.

a) DNA can be transfected into mammalian cells with appropriate selection markers by a variety of techniques, calcium phosphate precipitation, polyethylene

glycol, protoplast-fusion, etc..

b) DNA fragments corresponding to genes can be cloned into expression vectors for *E. coli*, yeast- or mammalian cells and the resultant proteins purified.

5 c) The proviral DNA can be "shot-gunned" (fragmented) into procaryotic expression vectors to generate fusion polypeptides. Recombinant producing antigenically competent fusion proteins can be identified by simply screening the recombinants with antibodies against LAV
10 antigens.

The invention also relates more specifically to cloned probes which can be made starting from any DNA fragment according to this invention, thus to recombinant
15 DNAs containing such fragments, particularly any plasmids amplifiable in procaryotic or eucaryotic cells and carrying said fragments.

Using the cloned DNA fragments as a molecular hybridization probe - either by marking with radionucleotides or with fluorescent reagents - LAV virion RNA may be
20 detected directly in the blood, body fluids and blood products (e.g. of the antihemophylic factors such as factor VIII concentrates) and vaccines, i.e. hepatitis B vaccine. It has already been shown that whole virus can be detected in culture supernatants of LAV producing cells. A
25 suitable method for achieving that detection comprises immobilizing virus onto said a support e.g. nitrocellulose filters, etc., disrupting the virion and hybridizing with labelled (radiolabelled or "cold" fluorescent- or enzyme-labelled) probes. Such an approach has already been
30 developed for Hepatitis B virus in peripheral blood (according to SCOTTO J. et al. Hepatology (1983), 3, 379-384).

Probes according to the invention can also be used for rapid screening of genomic DNA derived from the tissue
35 of patients with LAV related symptoms, to see if the proviral DNA or RNA is present in host tissue and other

tissues.

A method which can be used for such screening comprise the following steps : extraction of DNA from tissue, restriction enzyme cleavage of said DNA, electrophoresis of the fragments and Southern blotting of genomic DNA from tissues, subsequent hybridization with labelled cloned LAV proviral DNA. Hybridization in situ can also be used.

Lymphatic fluids and tissues and other non-lymphatic tissues of humans, primates and other mammalian species can also be screened to see if other evolutionary related retrovirus exist. The methods referred to hereabove can be used, although hybridization and washings would be done under non stringent conditions.

The DNA according to the invention can be used also for achieving the expression of LAV viral antigens for diagnostic purposes.

The invention also relates to the polypeptides themselves which can be expressed by the different DNAs of the inventions, particularly by the ORFs or fragments thereof, in appropriate hosts, particularly procaryotic or eucaryotic hosts, after transformation thereof with a suitable vector previously modified by the corresponding DNAs.

These polypeptides can be used as diagnostic tools, particularly for the detection of antibodies in biological media, particularly in sera or tissues of persons afflicted with pre-AIDS or AIDS, or simply carrying antibodies in the absence of any apparent disorders. Conversely the different peptides according to this invention can be used themselves for the production of antibodies, preferably monoclonal antibodies specific of the different peptides respectively. For the production of hybridomas secreting said monoclonal antibodies conventional production and screening methods are used. These monoclonal antibodies, which themselves are part of

the invention then provide very useful tools for the identification and even determination of relative proportions of the different polypeptides or proteins in biological samples, particularly human samples containing
5 LAV or related viruses.

Thus all of the above peptides can be used in diagnostics as sources of immunogens or antigens free of viral particles, produced using non-permissive systems, and thus of little or no biohazard risk.

10 The invention further relates to the hosts (prokaryotic or eucaryotic cells) which are transformed by the above mentioned recombinants and which are capable of expressing said DNA fragments.

Finally it also relates to vaccine compositions
15 whose active principle is to be constituted by any of the expressed antigens, i.e. whole antigens, fusion polypeptides or oligopeptides in association with a suitable pharmaceutical or physiologically acceptable carrier.

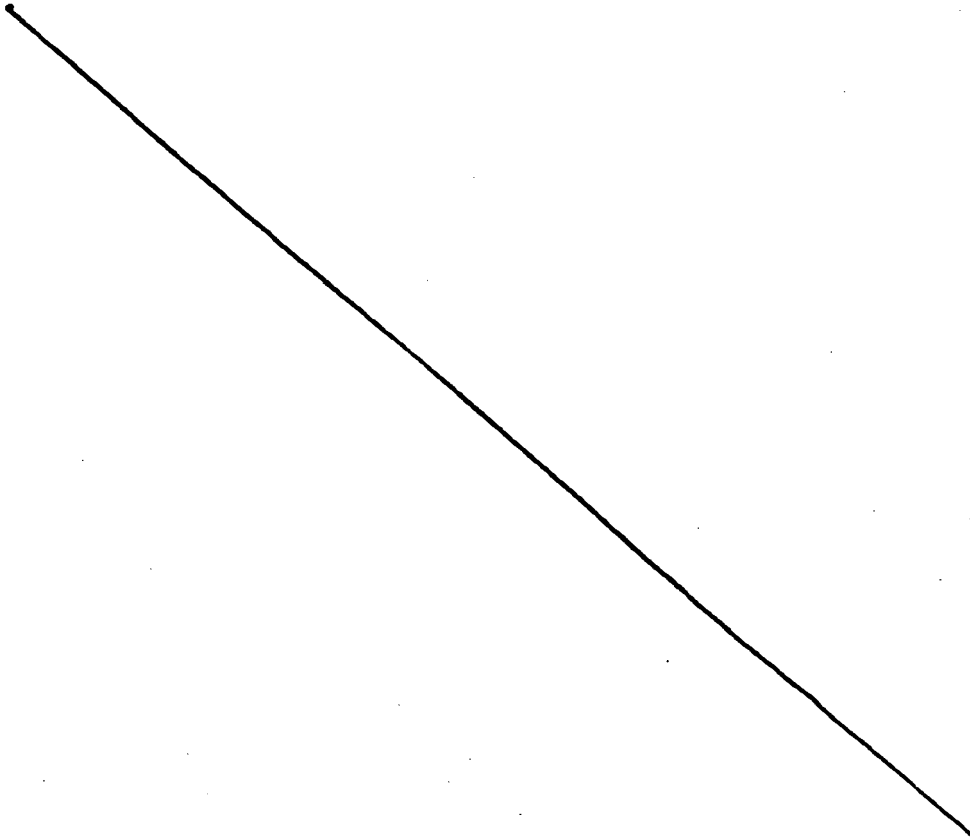
Preferably the active principles to be considered
20 in that field consist of the peptides containing less than 250 aminoacid units, preferably less than 150 as deducible for the complete genomes of LAV, and even more preferably those peptides which contain one or more groups selected from N-X-S and N-X-T as defined above. Preferred peptides
25 for use in the production of vaccinating principles are peptides (a) to (f) as defined above. By way of example having no limitative character, there may be mentioned that suitable dosages of the vaccine compositions are those which enable administration to the host.
30 particularly human host ranging from 10 to 500 micrograms per kg, for instance 50 to 100 micrograms per kg.

For the purpose of clarity figs. 19 to 25 are added. reference may be made thereto in case of difficulties of reading blurred parts of figs. 4 to 12.

Needless to say that figs. 19-28 are merely a reiteration of the whole DNA sequence of the LAV genome.

Finally the invention also concerns vectors for the transformation of eucaryotic cells of human origin, particularly lymphocytes, the polymerases of which are capable of recognizing the LTRs of LAV. Particularly said vectors are characterized by the presence of a LAV LTR therein, said LTR being then active as a promoter enabling the efficient transcription and translation in a suitable host of the above defined, of a DNA insert coding for a determined protein placed under its controls.

Needless to say that the invention extends to all variants of genomes and corresponding DNA fragments (ORFs) having substantially equivalent properties, all of said genomes belonging to retroviruses which can be considered as equivalents of LAV.



CLAIMS

1. A DNA fragment of LAV extending from nucleotide position 236 to nucleotide position 1759.

2. A DNA fragment of LAV extending from nucleotide position 1555 to nucleotide position 5086.

3. A DNA fragment of LAV extending from nucleotide position 5670 to nucleotide position 8132.

4. A vector containing a DNA fragment according to any of claims 1 to 3.

5. Peptide corresponding to any of those encoded by the nucleotide sequences which extend respectively between the following positions :

a) from about 6095 to about 6200

b) " " 6260 " " 6310

c) " " 6390 " " 6440

d) " " 6485 " " 6620

e) " " 6860 " " 6930

f) " " 7535 " " 7630

6. Peptide characterized by a sequence of aminoacids deducible from LAV DNA the terminal aminoacids of which extend between the following positions with respect to the lysine (position 1) coded by the AAA at position 5670-5672 in the LAV DNA.

8-23 aminoacids inclusive

83-78 " "

82-90 " "

97-123 " "

127-183 " "

197-201 " "

239-294 " "

300-327 " "

334-381 " "

397-424 " "

466-500 " "

510-523 " "

551-577 " "

594-603 - -
 621-630 - -
 657-678 - -
 719-758 - -
 780-803 - -

or any combination of these peptides.

7. Peptide corresponding to the aminoacid sequences deducible from LAV DNA and the terminal aminoacids of which are positionned at the positions hereafter counted from the Met at position 1 coded by the ATG sequence at nucleotide positions 280-2 :

12-32 aminoacids inclusive

	37-48	-	-
	49-79	-	-
15	88-153	-	-
	158-185	-	-
	178-188	-	-
	200-220	-	-
	226-234	-	-
20	239-264	-	-
	268-331	-	-
	352-361	-	-
	377-390	-	-
	398-432	-	-
25	437-484	-	-
	482-498	-	-

and combination of said peptides.

8. Diagnostic means containing any of the DNA fragments of any of claims 1 to 3.

9. Diagnostic means containing any of the peptides of any of claims 4 to 8.

10. Vaccine compositions containing any of the peptides according to any of claims 4 to 8 in association with a pharmaceutical vehicle.

End of transmission

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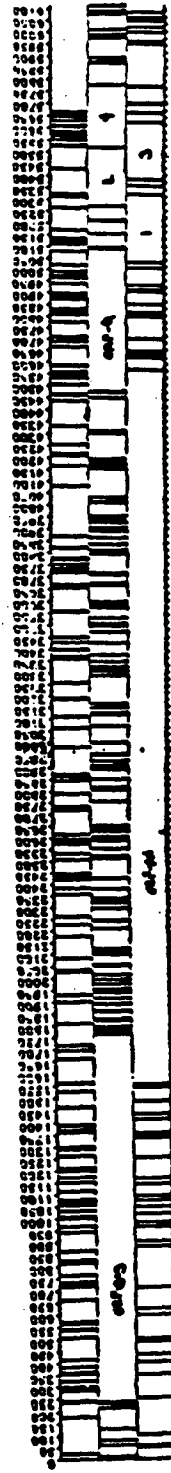


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Fig 4

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CAGAGGAGACCAAGAAATGAGGAGTAGATCTAGACTAGAGCCCTGGAAGCATCCAGGAAGTCAGCCTAA
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P S L F H N K S L R H L L W O E L A E T A T K T S
O V C F T T K A L G I S Y G R K K R R Q R R R P P
K F V S O O K P * A S P M A G R S G D S D E D L I
CCAAGTTTGTTCACAACAAAGCCTTAGGCATCTCCTATGGCAGGAAGAAGCGGAGACAGCGACCAAGACCTCC
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S T C N A T Y T N S N S S I S S S N N N S N S C V
V H V M O P I Q I A I A A L V V A I I I A I V V W
Y * C N L Y K * Q * Q H * * * O * * * O * L C C
AGTACATGTAATGCAACCTATACAAATAGCAATAGCAGCATTAGTAGTAGCAATAATAATAGCAATAGTTGTGTG
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I * U V N * * T N R K S R R O W O * E * R R N I S
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* T G * L I D * * K E O K T V A M R V K E K Y U
AATAGACAGTTAATTGATAGACTAATAGAAAGAGCAGAGACAGTGGCAATGAGAGTGAAGGAGAATATCACC
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L M I C S A T E K L W V T V Y Y G V P V W K E A
TATTGATGATCTGTAGTCTACAGAAAATGTGGGTACAGTCTATTATGGGGTACCTGTGTGGAAGGAAGCAAC
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K Y I * F G P H N P V Y P U T P T H K K * Y * * M
G T * C L G H T C L C T H R P O P T R S S I G Y C
V H N V W A T H A C V P T D P N P O E V V L V N
ACGTACATAATGTTTGGGCCACACATGCCTGTGTACCCACAGACCCCAACCCACAAGAAGTAGTATTGCTAAATGT
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C H R I * S V Y G I K A * S H V * N * P H S V L V
A * G Y N U F M G S K P K A N C K I N P T L C * F
H E D I I S L * D O S L K P C V K L T P L C V S L
TGCATGAGGATAAATCAGTTTATGGGATCAAAGCCTAAAGCCATGTGTAATAATTAACCCCACTCTGTGTAGTT
5910 5920 5930 5940 5950 5960 5970

I P I V V A G K * * W R K E R * K T A L S I S A O
Y O * * * K G H D D G E R R D K K I L F O Y O H K
T M S S S G E N N M E K G E I K N C S F N I S T
ATACCAATAGTACGCGGGAAATGATGATGAGAAAGCAGAGATAAAAACTGCTCTTTCAATATCAGCACAC
6130 6140 6150 6160 6170 6180 6190

L I * Y O * I M I L P A I R * U V V T P O S L H R
* Y N T H R * * Y Y O L Y V D K L * H L S H Y T G
U I I P I D V D T T S Y T L T S C N T S V I T O
TTGATATAATACCAATAGATAATGATACTACCAGCTATACGTTGACAAGTTGTAACAGCTCAGTCATTACACAGC
6250 6260 6270 6280 6290 6300 6310

P * L V L * F * N V I I K * S * E * D * H * V * O * M * S * A

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S O P K T A C T T C Y C K K C C F H C
V S L K L L V P L A I V K S V A F I A
CAGGAAGTCAGCCTAAAACTGCTTGTACCACTTGTATTGTAAAAAGTGTTCATTG
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A T K T S S P Q S D S S S F S I K A V S
U R R R P P Q G S G T H C V S L S K O * V
S D E D L L K A V R L I K F L Y Q S S K *
AGCGACGAAGACCTCCTCAAGGCAGTCAGACTCATCAAGTTTCTCTATCAAAGCAGTAAGT
5470 5480 5490 5500 5510 5520

S N S C V V H S N H R I * E N I K T K K
I A I V V W S I V I I E Y R K I L R O R K
* Q * L C G P * * S * N I G K Y * D K E K
TAGCAATAGTTGTGTGGTCCATAGTAATCATAGAATATAGGAAAATATTAAGACAAAGAAA
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R R N I S T C G D G G G N G A P C S L G
K G E I S A L V E H G V E H G H A P W D
K E K Y Q H L W R W G W K W G T M L L G I
AAGGAGAATATCAGCACTTGTGGAGATGGGGGTGGAATGGGGCACCATGCTCCTTGGGA
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C G F K Q P P L Y F V H Q M L K H M I Q
V E G S N H H S I L C I R C * S I * Y R
V W K E A T T T L F C A S D A K A Y D T E
TGTGGAAGGAAGCAACCACCACTCTATTTTGTGCATCAGATGCTAAAGCATATGATACAG
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TAGTATTGGTAAATGTGACAGAAAATTTTAACATGTGGAAAAATGACATGGTAGAACAGA
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H S V L V * S A L I W G * L L I P I V V
T L C * F K V H * F G E C Y * Y O * *
P L C V S L K C T D L G N A T N T N S S N
CACTCTGTGTTAGTTTAAAGTGCAGTGTATTTGGGGATGCTACTAATACCAATAGTAGTA
6070 6080 6090 6100 6110 6120

S I S A Q A * E V R C P K N M H F F I N
O Y O H K H K R * G A E R I C I F L * T
F N I S T S I R G K V Q K E Y A F F Y K L
TCAATATCAGCACAAGCATAAGAGGTAAGGTCCAGANAGAATATGCATTTTTTTATAAAC
6190 6200 6210 6220 6230 6240

S L H R P V Q R Y P L S Q F P Y I I V
S H Y T G L S K G I L * A N S H T L L C
S V I T Q A C P K V S F E P I P I H Y C A
CAGTCATTACACAGGCTGTCCAAAGGTATCCTTTGAGCCAATTCCCATACATTATTGTC
6310 6320 6330 6340 6350 6360

V Q M S A Q Y N V H * F L G Q * Y Q L N

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P G A F C D S * * * * * V J * H R T M Y K C *
P A G F A I L K C N * * * * * F * * * * * G P C T * * * * *
CCCCGGCTGGTTTTCGATTCTAAAATGTAATAAAGACGTTCAATGGGAACAGGACCATGTACAAATGTCAG
6370 6380 6390 6400 6410 6420 6430

C C * M A V * Q K K R * * L D L P I S O T N L K I
A V E W O S S R R R G S N * I C O F H K O C * N
L L * * * * * L A E E E V V I R S A * * * * * D N A K Y
TCTGTTCAATGGCAGTCTAGCAGAAGAAGAGGTAGTAATTAGATCTCCCAATTTACAGACAATGCTAAAGCC
6490 6500 6510 6520 6530 6540 6550

P T T I G E K V S V S R G D O G E H L L O * E K *
O G O Y K K K Y P Y P E G T R E S I C Y N P K N
N * * * * * R K S I R I O R G P G R A F V T I G K I
CCAACAACAATACAAGAAAAAGTATCCGTATCCAGAGGGGACCAGGGAGAGCATTGTGTACAATAGCAAAAAATA
6610 6620 6630 6640 6650 6660 6670

M P L * N R * L A N * E N N L E I I K O * S L S G
C H F K T O S * O I K R T I W K * * N N N L * A
* * * * * L K O I A S K L R E O F G N * * * * * I I F K O
ATGCCACITTTAAACAGATAGCTAGCAATTAAGAGAACAATTTGGAATAATAAAACAATAATCTTTAAGCAA
6730 6740 6750 6760 6770 6780 6790

I G N F S T V I O H N C L I V L G L I V L G V L K
H G I F L L * F N T T V * * Y L V * * Y L E Y *
G E F F Y C * * * * * Q L F * * * * * W F * * * * * W S T E
GAGGGGAATTTCTACTGTAATTCACACAAGTGTAAATAGTACTTGGTTAATAGTACTTGGAGTACTGAAC
6850 6860 6870 6880 6890 6900 6910

E * N N L * T C G R K * E K O C M P L P S A D K L
N K T I Y K H V A G S R K S N V C P S H Q R T H *
I K O F I N M W O E V G K A M Y A P P I S G O I
GAATAAAACAATTTATAAACATGTGGCAGGAAGTAGAAAAAGCAATGTATGCCCTCCCATCAGCGGACAAATTA
6970 6980 6990 7000 7010 7020 7030

V I T T H G P R S S D L E E E I * G T I G E V N Y
* * * * * O O W V R D L O T W R R R Y E G O L E K * I I
N N N * * * * * E I F R P G G G D H R O N W R S E L
GTAATAACAACAATGGGTCGAGATCTTCAGACCTGGAGGAGGAGATATGAGGGACAATTTGAGAAGTGAATTA
7090 7100 7110 7120 7130 7140 7150

P R O R E E W C R E K K E O W E * E L C S L G S W
O G K E K S G A E R K K S S G N R S F V P W V L
K A K R R V V O R E K R A V G I G A L F L G F L
CCAAGGCAAAAGAGAAGTGGTGCAGAGAGAAAAAGAGCAGTGGGAATAGGAGCTTTGTTCTTGGCTTTC
7210 7220 7230 7240 7250 7260 7270

Y R P D N Y C L V * C S S R T I C * G L L R R N S
T G O T I I V H Y S A A A E O F A E G Y * G A T
O A R O L L S G I V O O O N N L L R A I E A O O
TACAGGCCAGACAATTTGCTGCTATAGTGCACGACGAGAACAATTTGCTGAGGGCTATTGAGGCCCAACAGC
7330 7340 7350 7360 7370 7380 7390

E S A L W K D T * R I N S S W G F G V A L E N S F

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H T M Y K C H S T M Y T M Y * A S S I N S
G P C T N V S T V O C T H G I R P V V S T U L
AACAGGACCATGTACAAATGTCAGGACAGTACAATGTACACATGGAATTAGGCCAGTAGTATCAACTCAAC
6420 6430 6440 6450 6460 6470 6480

I S O T M L K P * * Y S * T N L * K L I V U O
O F H R O C * N H N S T A E P I C K N * L Y K T
N F T D N A K T I I V O L N O S V E I N C T R P
CAATTTACAGACAATGCTAAAACCATAATAGTACAGCTGAACCAATCTGTAGAAATTAATTGTACAAGAC
6540 6550 6560 6570 6580 6590 6600

F H L L O * E K * E I * O K H I V T L V F O N G
S I C Y N P K N R K Y E T S T L * H * * S K M E
A F V T I G K I G N M R O A H C N I S R A K W N
AGCATTGTGTACAAATAGGAAAAATAGGAAATATGAGACAAGCACATTGTAAACATTAGTAGAGCAAAATGCA
6660 6670 6680 6690 6700 6710 6720

I I K O * S L S N P O E G T O K L * R T V L I V
* * N * V L * A I L R R G G P R N C N A O F * L W
N K T I I F K O S S G G D P E I V T H S F N C G
TAATAAAACAATAATCTTTAAGCAATCCTCAGGAGGGGACCCAGAAATTGTAAACGCACAGTTTAAATTGTC
6780 6790 6800 6810 6820 6830 6840

G L I V L G V L K G Q I T L K E V T O S M S H A
V * * Y L E Y * R V K * M * R K * H N H T P M O
F N S T W S T E G S N N T E G S O T I T L P C R
GTTTAATAGTACTTGGAGTACTGAAGGGTCAAAATAACACTGAAGGAAGTGACACAATCACACTCCCATGCA
6900 6910 6920 6930 6940 6950 6960

M P L P S A D K L D V H O I L O G C Y * O E M V
C P S H O R T N * M F I K Y Y R A A I N K R W W
A P P I S G O I R C S S N I T G L L L T R D G G
TGCCCCCTCCCATCAGCGGACAAATTAGATGTTTCATCAAAATATTACAGGCTGCTATTAACAAGAGATGGTG
7020 7030 7040 7050 7060 7070 7080

* G T I G E V N Y I N I K * * K L N H * E * H P
E G O L E K * I I * I * S S K N * T I R S S T H
R O N W R S E L Y K Y K V V K I E P L G V A P T
GAGGCACAATTGGAGAAGTGAATTATATAAATATAAAGTAGTAAAAATTGAACCATTAGGAGTAGCACCCA
7140 7150 7160 7170 7180 7190 7200

* E L C S L G S W E O O E A L W A H G O * R * R
R S F V P W V L G S S R K H Y G R T V N D A O G
G A L F L G F L G A A G S T M G A R S M T L T V
AGGAGCTTTGTTCTTGGTTCTTGGGAGCAGCAGGAAGCACTATGGGCGCACGGTCAATGACGCTGACGG
7260 7270 7280 7290 7300 7310 7320

* G L L R R N S I C C N S O S G A S S S S R O
A E G Y * G A T A S V A T H S L G H O A A P C K
L R A I E A O O H L L O L T V W G I K U L O A R
CTGAGCGCTATTGAGCGGCAACAGCATCTGTTCAACTCACAGTCTGGGGCATCAAGCAGCTCCAGGCA
7380 7390 7400 7410 7420 7430 7440

G V A L E N S F A P L L C L G * L V G V I N L

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V P G C G K I P K G S T A P G D L G L L A K T H
I L A V E R Y L K D O G L L G I W G C S G K L I
GAATCCTGGCTGTCGAAGAATACCTAAGGATCAACAGCTCCTGGGGATTGGGGTTGCTCTGGAAAACCTCATI
7450 7460 7470 7480 7490 7500 7510

H N R F G I T * P G W S G T E K L T I T O A * Y I
G T O L E * H D L D G V G D R N * O L H K L N T
E O I W N N Y T W M E W D R E I N N Y T S L I H
TGAACAGATTGGGAATAACATGACCTGGATGGAGTGGGACAGAGAAATTAACAATTACACAAGCTTAATACAT
7570 7580 7590 7600 7610 7620 7630

N Y * H * I N G O V C G I G L T * G I G C G I * K
I I G I R * M G K F V E L V * W N K L A V V Y K
L L E L D K W A S L W N W F N I T N W L W Y I K
AATTATTGGAATTAGATAAATGGGCAAGTTTGTGGAATTGCTTAACATAACAAATTGGCTGTGGTATATAAAA
7690 7700 7710 7720 7730 7740 7750

L L Y F L * * I E L G R D I H H Y R F R P T S Q P
C C T F Y S E * S * A G I F T I I V S D P P P N
A V L S I V N R V R O G Y S P L S F O T H L P T
TTGCTGTACTTTCTATAGTGAATAGAGTTAGGCAGGATATTACCATTATCGTTTCAGACCCACCTCCCAACC
7810 7820 7830 7840 7850 7860 7870

R E T E T D P F D * * T D P * H L S G T I C G A L
E R U W Q I H S I S E R I L S T Y L G R S A E P
R D R D R S I R L V N G S L A L I W D D L R S L
AGAGACAGACAGACAGATCCATTGATTAGTGAACGATCTTAGCATTATCTGGGACGATCTGCGGAGCCTT
7930 7940 7950 7960 7970 7980 7990

T R I V E L L G K R G W E A L K Y W W N L L O Y N
R G L W N F W D A G C G K P S N I G G I S Y S I
E D C G T S G T O G V G S P O I L V E S P T V L
ACGAGGATTGTGGAACCTTCTGGGACGCAGGGGTGGGAAGCCCTCAAATATTGCTGGAATCTCTACAGTATTC
8050 8060 8070 8080 8090 8100 8110

A I A V A E G T D R V I E V V O G A C R A I R H I
P * J * L R G O I G L * K * Y K E L V E L F A T
H S S S * G D R * G Y R S S T R S L * S Y S P H
GCCATAGCAGTAGCTGAGGGGACAGATAGGCTTATAGAAGTAGTACAAGGAGCTTGTAGAGCTATTGCCACAT
8170 8180 8190 8200 8210 8220 8230

G W O V Y K K * C G W H A Y C K G K V E T S * A S
G G K W S K S S V V G W P T V R E R M R R A E P
Y A S G O K V V W L D G L L * G K E * D E L S O
GGTGGCAAGTGGTCAAAAAGTAGTGTGGTTGGATGGCCTACTGTAAGGCAAGAATGAGACGAGCTGAGCCAG
8290 8300 8310 8320 8330 8340 8350

S N H K * O Y S S Y O C C L C L A R S T R G G G C
A I T S S N T A A T N A C A W L F A O E E E E
U S O V A I U D L P M L L V P G * K H K R R R S
ACCAATCACAAGTAGCAATACAGCAGCTACCAATGCTGCTTGTGCTTGGCTTGAAGGACATAGAGGAGGAGGAGG
8410 8420 8430 8440 8450 8460 8470

U G S C R S * P L F K R K G G T G

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A K T H L H H C C A L E C * L E * * I S
K L I C T T A V P W V A S W S W S L
CTGGAAACTCATTTGCACCACTGCTGTCCTTGGATGCTAGTTGGAGTAATAAATCTC
7510 7520 7530 7540 7550 7560

O A * Y I P * L K N R K T S K K R M N K
K L N T F L N * R I A K P A R K E * T R
S L I H S L I E E S O V O O E K N E O E
CAAGCTTAATACATTCCTTAATTGAAGAATCGCAAAACCAGCAAGAAAAGAATGAACAAG
7630 7640 7650 7660 7670 7680

C G I * K Y S * * * E A W * V * E * F
V V Y K N I H N D S R R L G R F K N S F
W Y I K I F I M I V G G L V G L / R / I V F
TGTGGTATATAAAATATTCATAATGATAGTAGGAGGCTTGGTAGGTTTAAGAATAGTTT
7750 7760 7770 7780 7790 7800

P T S O P R G D P T G P K E * K K K V E
P P P N P E G T R O A R R N R R R R W R
T H L P T P R G P D R P E G I E E E G G E
CCCACCTCCCAACCCGAGGGGACCCGACAGGCCCAAGGAATAGAAGAAGAAGGTGGAG
7870 7880 7890 7900 7910 7920

I C G A L C L F S Y H R L R D L L I V
S A E P C A S S A T T A * E T Y S * L *
L R S L V P L O L P P L E R L T L D C N
ATCTGCGGAGCCTTGTGCTCTTCAGCTACCACCGCTTGAGAGACTTACTCTTGATTGTA
7990 8000 8010 8020 8030 8040

L L O Y H S O E L K N S A V S L L N A T
S Y S I G V R N * R I V L L A C S M P O
P T V L E S G T K E * C C * L A O C H S
TCCTACAGTATTGGAGTCAGGAATAAGAATAGTGCTGTTAGCTTGCTCAATGCCACA
8110 8120 8130 8140 8150 8160

A I R H I P R R I R O G L E R I L L * D
L F A T Y L E E * D R A W K G F C Y K M
Y S P H T * K N K T G L G K D F A I R W
CTATTGCCACATACCTAGAAGAATAAGACAGGCTTGGAAAGGATTTTGTATAAGAT
8230 8240 8250 8260 8270 8280

T S * A S S R A G G S S I S R P G K T W
R A E P A A D G V G A A S R D L E K H G
E L S O O O * G W E O H L E T W K N M E
CGAGCTGAGCCAGCAGCAGATGGGGTGGGAGCAGCATCTCGAGACCTGGAAAAACATGG
8350 8360 8370 8380 8390 8400

R G C G G G F S S H T S G T F K T N D L
E E E E V G F P V T P C V P L R P M T Y
R R P R N Y F J S H L R Y L * D O * L T
AGCAGCAGGAGGCGGTTTCCAGTCACGCTCAGCTACCTTTAAGACCAATCACTTA
8450 8460 8470 8480 8490 8500 8510 8520

3 L P T B / 4
15/15 B / 4
S V G L P H T R L L

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D F A

Fig 19

10	20	30	40	50	60
AAGCTTGCCT	TGAGTGCCTC	AAGTAGTGTC	TGCCCCGTCTG	TTGTGTGACT	CTGGTAAC7A
70	80	90	100	110	120
GAGATCCCTC	AGACCCTTTT	AGTCAGTGTC	GAAAACTCT	AGCAGTGGCG	CCCCAACAGG
130	140	150	160	170	180
GACTTGAAAG	CGAAAGGGAA	ACCAGAGGAG	CTCTCTCGAC	GCAGGACTCG	GCTTGCTGAA
190	200	210	220	230	240
CGCGCCACGG	CAAGAGGCGA	GGGGAGGCGA	CTGGTGAGTA	CGCCAAAAAT	TTTGACTAGC
250	260	270	280	290	300
GGAGGCTAGA	AGGAGAGAGA	TGGGTGCGAG	AGCGTCAGTA	TTAAGCGGGG	GAGAATTAGA
310	320	330	340	350	360
TGGATCGGAA	AAAATTCGGT	TAAGGCCAGG	GGGAAAGAAA	AAATATAAAT	TAAACATAT
370	380	390	400	410	420
AGTATGGGCA	AGCAGGGAGC	TAGAACGATT	CGCTGTTAAT	CCTGGCCTGT	TAGAAACATC
430	440	450	460	470	480
AGAAGGCTGT	AGACAAATAC	TGGGACAGCT	ACAACCATCC	CTTCAGACAG	GATCAGAAGA
490	500	510	520	530	540
ACTTAGATCA	TTATATAATA	CAGTAGCAAC	CCTCTATTGT	GTGCATCAAA	GGATAGAGAT
550	560	570	580	590	600
AAAAGACACC	AAGGAAGCTT	TAGACAAGAT	AGAGGAAGAG	CAAAACAAAA	GTAAGAAAAA
610	620	630	640	650	660
AGCACAGCAA	GCAGCAGCTG	ACACAGGACA	CAGCAGCCAG	GTGAGCCAAA	ATTACCCTAT
670	680	690	700	710	720
AGTGCAGAAC	ATCCAGGGGC	AAATGGTACA	TCAGGGCATA	TCACCTAGAA	CTTTAAATGC
730	740	750	760	770	780
ATGGGTAAAA	GTAGTACAAG	AGAAGGCTTT	CAGCCCAGAA	GTGATACCCA	TGTTTTCAGC
790	800	810	820	830	840
ATTATCAGAA	GGAGCCACCC	CACAAGATTT	AAACACCATG	CTAAACACAG	TGGCGGGACA
850	860	870	880	890	900
TCAAGCAGCC	ATGCAAATGT	TAAAAGAGAC	CATCAATGAG	GAAGCTGCAG	AATGGGATAG
910	920	930	940	950	960
AGTGCATCCA	GTGCATGCAG	GGCCTATTGC	ACCAGGCCAG	ATGAGAGAAC	CAAGGGGAAG
970	980	990	1000	1010	1020
TGACATAGCA	GGAAC7ACTA	GTACCCTTCA	GGAACAAATA	GGATGGATGA	CAAATAATCC
1030	1040	1050	1060	1070	1080
ACCTATCCCA	G7AGGAGAAA	TTTATAAAAG	ATGGATAATC	CTGGGATTAA	ATAAAATAGT
1090	1100	1110	1120	1130	1140

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Fig 20

AAGAATCTAT	AGCCCTACCA	GCATTCTGGA	CATAAGACAA	GGACCAAAAG	AACCCTTTAG
1150	1160	1170	1180	1190	1200
AGACTATGTA	GACCGGTTCT	ATAAACTCT	AAGAGCCGAG	CAAGCTTCAC	AGGAGGTAAA
1210	1220	1230	1240	1250	1260
AAATTGGCATG	ACAGAAACCT	TGTTGGTCCA	AAATGCCAAC	CCAGATTGTA	AGACTATTTT
1270	1280	1290	1300	1310	1320
AAAAGCATTG	CGACCAGCAG	CTACACTAGA	AGAAATCATG	ACAGCATGTC	AGGGAGTGGG
1330	1340	1350	1360	1370	1380
AGGACCCGGC	CATAAGGCAA	GAGTTTGGC	TGAAGCAATG	AGCCAAGTAA	CAAATTCACC
1390	1400	1410	1420	1430	1440
TACCATAATG	ATGCAAAGAG	GCAATTTTAG	GAACCAAAGA	AAGATTGTTA	AGTGTTCCTA
1450	1460	1470	1480	1490	1500
TTGTGGCAAA	GAAGGGCACA	TAGCCAGAAA	TTGCAGGGCC	CCTAGGAAAA	AGGGCTGTTG
1510	1520	1530	1540	1550	1560
GAAATGTGGA	AAGGAAGGAC	ACCAAATGAA	AGATTGTACT	GAGAGACAGG	CTAATTTTTT
1570	1580	1590	1600	1610	1620
AGGGAAGATC	TGGCCTTCCT	ACAAGGGAAG	GCCAGGGAAT	TTTCTTCAGA	GCAGACCAGA
1630	1640	1650	1660	1670	1680
GCCAACAGCC	CCACCAGAAG	AGAGCTTCAG	GTCTGGGGTA	GAGACAACAA	CTCCCTCTCA
1690	1700	1710	1720	1730	1740
GAAGCAGGAG	CCGATAGACA	AGGAAGTGTG	TCCTTTAACT	TCCCTCAGAT	CACTCTTTGG
1750	1760	1770	1780	1790	1800
CAACGACCCC	TCGTCACAAT	AAAGATAGGG	GGGCAACTAA	AGGAAGCTCT	ATTAGATACA
1810	1820	1830	1840	1850	1860
GGAGCAGATG	ATACAGTATT	AGAAGAAATG	AGTTTGCCAG	GAAGATGGAA	ACCAAAAAATG
1870	1880	1890	1900	1910	1920
ATAGGGGGAA	TTGGAGGTTT	TATCAAAGTA	AGACAGTATG	ATCAGATACT	CATAGAAATC
1930	1940	1950	1960	1970	1980
TGTGGACATA	AAGCTATAGG	TACAGTATTA	GTAGGACCTA	CACCTGTCAA	CATAATTGGA
1990	2000	2010	2020	2030	2040
AGAAATCTGT	TGACTCAGAT	TGGTTGCACT	TTAAATTTTC	CCATTAGTCC	TATTGAAACT
2050	2060	2070	2080	2090	2100
GTACCAGTAA	AATTAAAGCC	AGGAATGGAT	GGCCCAAAAG	TTAAACAATG	GCCATTGACA
2110	2120	2130	2140	2150	2160
GAAGAAAAAA	TAAAAGCATT	AGTAGAAATT	TGTACAGAAA	TGCAAAAGGA	AGGGAAAAAT
2170	2180	2190	2200	2210	2220
TCAAAAAATTG	GGCCTGAAAA	TCCATACAAT	ACTCCAGTAT	TTGCCATAAA	GAAGAAAAAC
2230	2240	2250	2260	2270	2280
AGTACTAAAT	CGAGAAAAAT	AGTAGATTTT	AGAGAACTTA	ATAAGAGAAC	TCAAGACTTC
2290	2300	2310	2320	2330	2340
TGGGAAGTTC	AATTAGGAAT	ACCACATGCC	GCAGGGTTAA	AAAAGAAAAA	ATCAGTAACA

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D F A

2410 2420 2430 2440 2450 2460
 ACTGCATT TA CCATACCTAG TATAACAAT GAGACACCAG GGATTAGATA TCAGTACAAT
 2470 2480 2490 2500 2510 2520
 GTGCTTCCAC AGGGATGGAA AGGATCACCA GCAATATTCC AAAGTAGCAT GACAAAAATC
 2530 2540 2550 2560 2570 2580
 TTAGAGCCTT TTAGAAAAACA AAATCCAGAC ATAGTTATCT ATCAATACAT GGATGATTTG
 2590 2600 2610 2620 2630 2640
 TATGTAGGAT CTGACTTAGA AATAGGGCAG CATAGAACAA AAATAGAGGA GCTGAGACAA
 2650 2660 2670 2680 2690 2700
 CATCTGTTGA GGTGGGGACT TACCACACCA GACAAAAAAC ATCAGAAAGA ACCTCCATTG
 2710 2720 2730 2740 2750 2760
 CTTTGGATGG GTTATGAACT CCATCCTGAT AAATGGACAG TACAGCCTAT AGTGCTGCCA
 2770 2780 2790 2800 2810 2820
 GAAAAAGACA GCTGGACTGT CAATGACATA CAGAAGTTAG TGGGAAAATT GAATTGGGCA
 2830 2840 2850 2860 2870 2880
 AGTCAGATTT ACCCAGGGAT TAAAGTAAGG CAATTATGTA AACTCCTTAG AGGAACCAAA
 2890 2900 2910 2920 2930 2940
 GCACTAACAG AAGTAATACC ACTAACAGAA GAAGCAGAGC TAGAACTGCC AGAAAACAGA
 2950 2960 2970 2980 2990 3000
 GAGATTCTAA AAGAACCAGT ACATGGAGTG TATTATGACC CATCAAAAGA CTTAATAGCA
 3010 3020 3030 3040 3050 3060
 GAAATACAGA AGCAGGGGCA AGGCCAATGG ACATATCAAA TTTATCAAGA GCCATTTAAA
 3070 3080 3090 3100 3110 3120
 AATCTGAAAA CAGGAAAAATA TGCAAGAACC AGGGGTGCCC AACTAATGA TGTAAAACAA
 3130 3140 3150 3160 3170 3180
 TTAACAGAGG CAGTGCAAAA AATAACCACA GAAAGCATAG TAATATGGGG AAAGACTCCT
 3190 3200 3210 3220 3230 3240
 AAATTTAAAC TACCCATACA AAAGGAAACA TGGGAAACAT GGTGGACAGA GTATTGGCAA
 3250 3260 3270 3280 3290 3300
 GCCACCTGGA TTCCTGAGTG GGAGTTTGTC AATACCCCTC CTTTAGTGAA ATTATGGTAC
 3310 3320 3330 3340 3350 3360
 CAGTTAGAGA AAGAACCCTAT AGTAGGAGCA GAAACGTTCT ATGTAGATGG GGCAGCTAGC
 3370 3380 3390 3400 3410 3420
 AGGGAGACTA AATTAGGAAA AGCAGGATAT GTTACTAATA GAGGAAGACA AAAAGTTGTC
 3430 3440 3450 3460 3470 3480
 ACCCTAACTG ACACAACAAA TCAGAAGACT GAGTTACAAG CAATTCTATCT AGCTTTGCCAG
 3490 3500 3510 3520 3530 3540
 GATTCGGGAT TAGAAGTAAA TATAGTAACA GACTCACAAT ATGCATTAGG AATCATTCAA
 3550 3560 3570 3580 3590 3600
 GCACAACCAG ATAAAAGTGA ATCAGAGTTA GTCAATCAAA TAATAGAGCA CTTAATAAAA
 3610 3620 3630 3640 3650 3660

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Fig 22

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3670	3680	D F A 3690	3700	3710	3720
GTAGATAAAT	TAGTCAGTGC	TGGAATCAGG	AAAGTACTAT	TTTGTAGATGG	AATAGAT
3730	3740	3750	3760	3770	3780
GCCCAAGATG	AACATGAGAA	ATATCACAGT	AATTGGAGAG	CAATGGCTAG	TGATTTTAAC
3790	3800	3810	3820	3830	3840
CTGCCACCTG	TAGTAGCAAA	AGAAATAGTA	GCCAGCTGTC	ATAAATGTCA	GCTAAAACGA
3850	3860	3870	3880	3890	3900
GAAGCCATGC	ATGGACAAGT	AGACTGTAGT	CCAGGAATAT	GGCAACTAGA	TTGTACACAT
3910	3920	3930	3940	3950	3960
TTAGAAGGAA	AAGTTATCCT	GGTAGCAGTT	CATGTAGCCA	GTGGATATAT	AGAAGCAGAA
3970	3980	3990	4000	4010	4020
GTTATTCCAG	CAGAAACAGG	GCAGGAAACA	GCATACTTTC	TTTTAAAATT	AGCAGGAAGA
4030	4040	4050	4060	4070	4080
TGGCCAGTAA	AAACAATACA	TACAGACAAT	GGCAGCAATT	TCACCAGTAC	TACGGTTAAG
4090	4100	4110	4120	4130	4140
GCCGCCCTGTT	GGTGGGCGGG	AATCAAGCAG	GAATTTGGAA	TTCCCTACAA	TCCCCAAAGT
4150	4160	4170	4180	4190	4200
CAAGGAGTAG	TAGAATCTAT	GAATAAGAA	TTAAAGAAAA	TTATAGGCCA	GGTAAGAGAT
4210	4220	4230	4240	4250	4260
CAGGCTGAAC	ATCTTAAGAC	AGCAGTACAA	ATGGCAGTAT	TCATCCACAA	TTTTAAAAGA
4270	4280	4290	4300	4310	4320
AAAGGGGGGA	TTGGGGGGTA	CAGTGCAGGG	GAAAGAATAG	TAGACATAAT	AGCAACAGAC
4330	4340	4350	4360	4370	4380
ATACAAACTA	AAGAATTACA	AAAACAAATT	ACAAAAATTC	AAAATTTTCG	GGTTTATTAC
4390	4400	4410	4420	4430	4440
AGGCACAGCA	GAGATCCACT	TTGGAAAGGA	CCAGCAAAGC	TCCTCTGGAA	AGGTGAAGGG
4450	4460	4470	4480	4490	4500
GCAGTAGTAA	TACAAGATAA	TAGTGACATA	AAAGTAGTGC	CAAGAAGAAA	AGCAAAGATC
4510	4520	4530	4540	4550	4560
ATTAGGGATT	ATGGAAAACA	GATGGCAGGT	GATGATTGTG	TGGCAAGTAG	ACAGGATGAG
4570	4580	4590	4600	4610	4620
GATTAGAACA	TGGAAAAGTT	TAGTAAAACA	CCATATGTAT	GTTTCAGGGA	AAGCTAGGGG
4630	4640	4650	4660	4670	4680
ATGGTTTTAT	AGACATCACT	ATGAAAGCCC	TCATCCAAGA	ATAAGTTCAG	AAGTACACAT
4690	4700	4710	4720	4730	4740
CCCACTAGGG	GATGCTAGAT	TGGTAATAAC	AACATATTGG	GGTCTGCATA	CAGGAGAAAG
4750	4760	4770	4780	4790	4800
AGACTGGCAT	CTGGGTCAGG	GAGTCTCCAT	AGAATGGAGG	AAAAAGAGAT	ATAGCACACA
4810	4820	4830	4840	4850	4860
AGTAGACCCT	GAAGTAGCAG	ACCAACTAAT	TCATCTGTAT	TACTTTGACT	GTTTTTCAGA
4870	4880	4890	4900	4910	4920

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4930 4940 D F A4950 4960 4970 4980
 AGGACATAAC AAGGTAGGAT CTCTACAATA CTTGGCACTA CCAGCATTAA TAACACCAAA
 4990 5000 5010 5020 5030 5040
 AAAGATAAAG CCACCTTTTC CTAGTGTTAC GAAACTGACA GAGGATAGAT GGAACAAGCC
 5050 5060 5070 5080 5090 5100
 CCAGAAGACC AAGGGCCACA GAGGGAGCCA CACAATCAAT GGACACTAGA GCTTTTAGAG
 5110 5120 5130 5140 5150 5160
 GAGCTTAAGA ATGAAGCTGT TAGACATTTT CCTAGGATTT GGCTCCATGG CTTAGGGCAA
 5170 5180 5190 5200 5210 5220
 CATATCTATG AAACCTTATGG GGATACTTGG CCAGGAGTGG AAGCCATAAT AAGAATTCTG
 5230 5240 5250 5260 5270 5280
 CAACAACCTGC TGTATTATCCA TTTCAGAAAT GGGTGTGGAC ATAGCAGAAT AGGCGTTACT
 5290 5300 5310 5320 5330 5340
 CAACAGAGGA CAGCAAGAAA TGGAGCCAGT AGATCCTAGA CTAGAGCCCT GGAAGCATCC
 5350 5360 5370 5380 5390 5400
 AGGAAGTCAG CCTAAAACCTG CTTGTACCAC TTGCTATTGT AAAAAGTGT GCTTTCATTG
 5410 5420 5430 5440 5450 5460
 CCAAGTTTGT TTCACAACAA AAGCCTTAGG CATCTCCTAT GGCAGGAAGA AGCGGAGACA
 5470 5480 5490 5500 5510 5520
 GCGACGAAGA CCTCCTCAAG GCAGTCAGAC TCATCAAGTT TCTCTATCAA AGCAGTAAGT
 5530 5540 5550 5560 5570 5580
 AGTACATGTA ATGCAACCTA TACAAATAGC AATAGCAGCA TTAGTAGTAG CAATAATAAT
 5590 5600 5610 5620 5630 5640
 AGCAATAGTT GTGTGGTCCA TAGTAATCAT AGAATATAGG AAAATATTAA GACAAAGAAA
 5650 5660 5670 5680 5690 5700
 AATAGACAGG TTAATTGATA GACTAATAGA AAGAGCAGAA GACAGTGGCA ATGAGAGTCA
 5710 5720 5730 5740 5750 5760
 AGGAGAAATA TCAGCACTTG TGGAGATGGG GGTGGAAATG GGGCACCATG CTCCTTGGGA
 5770 5780 5790 5800 5810 5820
 TATTGATGAT CTGTAGTGCT ACAGAAAAAT TGTGGGTCAC AGTCTATTAT GGGGTACCTG
 5830 5840 5850 5860 5870 5880
 TGTGGAAGGA AGCAACCACC ACTCTATTTT GTGCATCAGA TGCTAAAGCA TATGATACAG
 5890 5900 5910 5920 5930 5940
 AGGTACATAA TGTTTGGGCC ACACATGCCT GTGTACCCAC AGACCCCAAC CCACAAGAAG
 5950 5960 5970 5980 5990 6000
 TAGTATTGCT AAATGTGACA GAAAATTTTA ACATGTGGAA AAATGACATG GTAGAACAGA
 6010 6020 6030 6040 6050 6060
 TGCATGAGGA TATAATCACT TTATGGGATC AAAGCCTAAA GCCATGTGTA AAATTAACCC
 6070 6080 6090 6100 6110 6120
 CACTCTGTGT TAGTTTAAAG TGCACATGATT TCCCGAATGC TACTAATACC AATAGTAGTA
 6130 6140 6150 6160 6170 6180

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ATACCAATAG TAGTAGCGGG GAAATGATGA TGGAGAAJGG AGAGATAAAA AACTCTCTCT

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6170 6200 6210 6220 6230 6240
 TCAATATCAG CACAAGCATA AGAGGTAAGG TGCAGAAAGA ATATGCATT TTTTATAAAC

6250 6260 6270 6280 6290 6300
 TTGATATAAT ACCAATAGAT AATGATACTA CCAGCTATAC GTTGACAAGT TGTAACACCT

6310 6320 6330 6340 6350 6360
 CAGTCATTAC ACAGGCCTGT CCAAAGGTAT CCTTTGAGCC AATTCCCATTA CATTATTCTG

6370 6380 6390 6400 6410 6420
 CCCCCGGCTGG TTTTGCGATT CTAAAATGTA ATAATAAGAC GTTCAATGGA ACAGGACCAT

6430 6440 6450 6460 6470 6480
 GTACAAATGT CAGCACAGTA CAATGTACAC ATGGAATTAG GCCAGTAGTA TCAACTCAAC

6490 6500 6510 6520 6530 6540
 TGCTGTTGAA TGGCAGTCTA GCAGAAGAAG AGGTAGTAAT TAGATCTGCC AATTTACACG

6550 6560 6570 6580 6590 6600
 ACAATGCTAA AACCATAATA GTACAGCTGA ACCAATCTGT AGAAATTAAT TGTACAAGAC

6610 6620 6630 6640 6650 6660
 CCAACAACAA TACAAGAAAA AGTATCCGTA TCCAGAGGGG ACCAGGGAGA GCATTTGTTA

6670 6680 6690 6700 6710 6720
 CAATAGGAAA AATAGGAAAT ATGAGACAAG CACATTGTAA CATTAGTAGA GCAAAATGGA

6730 6740 6750 6760 6770 6780
 ATGCCACTTT AAAACAGATA GCTAGCAAAT TAAGAGAACA ATTTGGAAAT AATAAAACAA

6790 6800 6810 6820 6830 6840
 TAATCTTTAA GCAATCCTCA GGAGGGGACC CAGAAATTGT AACGCACAGT TTTAATTCTG

6850 6860 6870 6880 6890 6900
 GAGGGGAATT TTTCTACTGT AATTCAACAC AACTGTTTAA TAGTACTTCC TTTAATAGTA

6910 6920 6930 6940 6950 6960
 CTTGGAGTAC TGAAGGGTCA AATAACACTG AAGGAAGTGA CACAATCACA CTCCCATGCA

6970 6980 6990 7000 7010 7020
 GAATAAAACA ATTTATAAAC ATGTGGCAGG AAGTAGGAAA AGCAATGTAT GCCCCCTCCA

7030 7040 7050 7060 7070 7080
 TCAGCGGACA AATTAGATGT TCATCAAATA TTACAGGGCT CCTATTAACA AGAGATCGTG

7090 7100 7110 7120 7130 7140
 GTAATAACAA CAATGGGTCC GAGATCTTCA GACCTGGAGG AGGAGATATC AGGGACAATT

7150 7160 7170 7180 7190 7200
 GGAGAAGTGA ATTATATAAA TATAAAGTAG TAAAAATTGA ACCATTAGCA GTAGCACCCA

7210 7220 7230 7240 7250 7260
 CCAAGGCAAA CAGAAGAGTG GTGCAGAGAG AAAAAAGAGC AGTGGGAATA GGAGCTTTGT

7270 7280 7290 7300 7310 7320
 TCCTTGGGTT CTTGGGAGCA GCAGGAAGCA CTATGGGCCC ACGGTCAATG ACGCTGACCG

7330 7340 7350 7360 7370 7380
 TACAGGCCAG ACAATTATTG TCTCGTATAG TGCAGCAGCA GAACAATTTG CTGAGGGCTA

7390 7400 7410 7420 7430 7440

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AGGGGCA ACAUCATCTG TTGCACTCA CAGTCTGGGG CATCAAGCAG CTCCAGGCAA

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7450 7460 7470 7480 7490 7500
GAATCCTGGC TGTGGAAAGA TACCTAAAGG ATCAACAGCT CCTGGGGATT TGGGGTTGCT

7510 7520 7530 7540 7550 7560
CTGGAAAACCT CATTTCGACC ACTGCTGTGC CTTGGAATGC TAGTTGGAGT AATAAATCTC

7570 7580 7590 7600 7610 7620
TGGAACAGAT TTGGAATAAC ATGACCTGGA TGGAGTGGGA CAGAGAAATT AACAAATTACA

7630 7640 7650 7660 7670 7680
CAAGCTTAAT ACATTCTTA ATTGAAGAAT CGCAAAACCA GCAAGAAAAG AATGAACAAG

7690 7700 7710 7720 7730 7740
AATTATTGGA ATTAGATAAA TGGGCAAGTT TGTGGAATTG GTTTAACATA ACAAATTGGC

7750 7760 7770 7780 7790 7800
TGTGGTATAT AAAAATATTG ATAATGATAG TAGGAGGCTT GCTAGGTTTA AGAATAGTTT

7810 7820 7830 7840 7850 7860
TTGCTGTACT TTCTATAGTG AATAGAGTTA GGCAGGGATA TTCACCATT ACGTTTCAGA

7870 7880 7890 7900 7910 7920
CCCACCTCCC AACCCCGAGG GGACCCGACA GGCCCGAAGC AATAGAAGAA GAAGGTGGAG

7930 7940 7950 7960 7970 7980
AGAGAGACAG AGACAGATCC ATTCGATTAG TGAACGGATC CTTAGCACTT ATCTGGGACC

7990 8000 8010 8020 8030 8040
ATCTGGGGAG CCTTGTGCCT CTTGAGCTAC CACCGCTTGA GAGACTTACT CTTGATTGTA

8050 8060 8070 8080 8090 8100
ACGAGGATTG TGGAACTTCT GGGACGCAGG GGCTGGGAAG CCCTCAAATA TTGGTGGAAAT

8110 8120 8130 8140 8150 8160
CTCCTACAGT ATTGGAGTCA GGAAGTAAAG AATAGTGCTG TTAGCTTGCT CAATGCCACA

8170 8180 8190 8200 8210 8220
GCCATAGCAG TAGCTGAGGG GACAGATAGG GTTATAGAAG TAGTACAAGG AGCTTGTAGA

8230 8240 8250 8260 8270 8280
GCTATTGCGC ACATACCTAG AAGAATAAGA CAGCGCTTGG AAAGGATTTT GCTATAAGAT

8290 8300 8310 8320 8330 8340
GGGTGGCAAG TGGTCAAAAA GTAGTGTGCT TGGATGGCCT ACTGTAAGGG AAAGAATGAG

8350 8360 8370 8380 8390 8400
ACGAGCTGAG CCAGCAGCAG ATGGGGTGGG AGCAGCATCT CGAGACCTGG AAAACATGG

8410 8420 8430 8440 8450 8460
AGCAATCACA AGTAGCAATA CAGCAGCTAC CAATGCTGCT TGTGCCTGGC TAGAAGCACA

8470 8480 8490 8500 8510 8520
AGAGGAGGAG GAGGTGGGTT TTCCAGTCAC ACCTCAGGTA CCTTTAAGAC CAATGACTTA

8530 8540 8550 8560 8570 8580
CAAGGCAGCT GTAGATCTTA GCCACTTTTT AAAAGAAAAG GGGGGACTGG AAGGGCTAAT

8590 8600 8610 8620 8630 8640
TCACTCCCAA CGAAGACAAG ATATCCTTGA TCTGTGGATC TACCACACAC AAGGCTAGTT

8650 8660 8670 8680 8690 8700

1725

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CCCTGATTGG CAGAACTACA CACCAGGGCC AGGGGTGCGA TATCCACTGA CCTTTGGATC
8710 8720 8730 8740 8750 8760
GTGCTACAAG CTAGTACCAG TIGAGCCAGA TAAGGTAGAA GAGGCCAATA AAGGAGAGAA
8770 8780 8790 8800 8810 8820
CACCAGCTTG TTACACCCTG TGAGCCTGCA TGAATGGAT GACCCTGAGA GAGAAGTCTT
8830 8840 8850 8860 8870 8880
AGAGTGGAGG TTTGACAGCC GCCTAGCATT TCATCACGTG CCCCAGAGAGC TGCATCCGCA
8890 8900 8910 8920 8930 8940
GTACTTCAAG AACTGCTGAG ATCGAGCTTG CTACAAGGGA CTTTCCGCTG GGGACTTTCC
8950 8960 8970 8980 8990 9000
AGCGAGGCGT GGCTGGGCG GAACTGGGGA GTGGCGAGCC CTCAGATGCT GCATATAACC
9010 9020 9030 9040 9050 9060
AGCTGCTTTT TGCCTGTACT GGGTCTCTCT GGTAGACCA GATTGAGCC TGGGAGCTCT
9070 9080 9090 9100 0 0
CTGGCTAACT AGGGAACCCA CTGCTTAAGC CTCAATAAAG CTT

Fig 26